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Clinical Morbidity Associated with *S. haematobium* Infection in Pre-School Age Children from an Endemic District in Zimbabwe.

Tariro L. Mduluza-Jokonya^{1,2}, Thajasvarie Naicker¹, Maritha Kasambala², Luxwell Jokonya^{3,1}, Arthur Vengesai^{1,3}, Herald Midzi², Emilia Choto², Kempton Musonza⁴, Simba Rusankaniko⁴, Elopy Sibanda⁵, Francisca Mutapi⁶, Takafira Mduluza²

¹Optics & Imaging, Doris Duke Medical Research Institute, College of Health Sciences, University of KwaZulu-Natal; KwaZulu-Natal, Durban, South Africa naickera@ukzn.ac.za

²Department of Biochemistry, University of Zimbabwe, P.O. Box MP 167, Mt Pleasant, Harare, Zimbabwe. mduluza@medic.uz.ac.zw ; tmduluza@yahoo.com

³Department of Surgery, College of Health Sciences, University of Zimbabwe, P.O. Box MP 167, Mt Pleasant, Harare, Zimbabwe. doclux@gmail.com

⁴ Department of Community Medicine, College of Health Sciences, University of Zimbabwe, P.O. Box MP 167, Mt Pleasant, Harare, Zimbabwe. srusakaniko@gmail.com

⁵ Twin Palms Medical Centre, 113 Kwame Nkrumah Avenue, Harare, Zimbabwe ensibanda@gmail.com

⁶Institute for Immunology and Infection Research and Centre for Immunity, Infection and Evolution, School of Biological Sciences, University of Edinburgh, Ashworth Laboratories, King's Buildings, Charlotte Auerbach Rd, EH9 3JT, Edinburgh f.mutapi@ed.ac.uk

Corresponding Author:

Tariro L Mduluza-Jokonya

Email: tljokonya@gmail.com

Abstract

Background: *Schistosoma haematobium* infection is associated with urogenital morbidity. There are limited studies reporting on *Schistosoma. haematobium* infected pre-school age children, particularly concerning the extent of morbidity. In this study we investigated *Schistosoma. haematobium* morbidity in infected pre-school age children and established their disease burden.

Methodology: Pre-school age children (1-5years) who were lifelong residents of the study area and had no other infections were included in the study. Participants underwent a physical examination with clinicians blinded from their infection status. Diagnosis of *Schistosoma. haematobium* was by urine filtration.

Results: The prevalence of *Schistosoma. haematobium* was 35.1%(146/416). The clinical features observed in patients with *Schistosoma. haematobium* were: wheezes (morbidity attributable factor (AF=93.9%), haematuria (AF=92.6%), ascites (AF=91.5%), atopy (AF=76.9%), inguinal lymphadenopathy(AF=68.4%), stunting (AF=38.2) , malnutrition (MUAC)(AF=20%) and weight for height scales (AF=5%). *Schistosoma. haematobium* infected children were at greater odds ratio of presenting with inguinal lymphadenopathy (AOR)=99.2(95% CI 24.2 to 854.5), wheezes in the chest (AOR=35.4 95% CI 15.3 to 94.2), Distended abdomen with ascites (AOR=23.9 95% CI 11.4 to 54), haematuria (AOR=12.6 95% CI 11.6 to 14.1), atopy history (AOR=5.6 95% CI 1.85 to 20.2), malnutrition (AOR=2.3 95% CI 1.4 to 3.2) and stunting (AOR= 1.9 95% CI 1.1 to 2.7).

Conclusion: The study is novel as it demonstrates for the first time clinical morbidity markers associated with *Schistosoma. haematobium* infection in pre-school age children. Furthermore the study adds scientific evidence to the call for inclusion of pre-school age children in schistosomiasis control programs. These morbidity markers highlight the need for early diagnosis and screening for *S. haematobium* in preschool age children.

Key words: Urogenital Schistosomiasis, morbidity, diagnosis, Pre-school aged children, neglected, *Schistosoma haematobium*

Introduction

Schistosomiasis is a neglected tropical disease and the 2nd most important parasitic disease in sub-Saharan Africa (1). There are five species of the trematodes that affect humans. These are *Schistosoma intercalatum*, *Schistosoma mekongi*, *Schistosoma japonicum*, *Schistosoma haematobium* and *Schistosoma mansoni*. *S. mansoni* and *S. japonicum* are responsible for intestinal schistosomiasis, while *S. haematobium* causes urinary schistosomiasis (2). In Zimbabwe the common species are *S. haematobium* and *S. mansoni* (3) with former being highly prevalent in many areas. Schistosomiasis morbidity has been extensively studied in adults and school aged children, but very little has been done on preschool age children (PSAC) (4–8). It has been noted that morbidity is directly proportional to infection intensity(5). Whereas the frequency of infection in PSAC has been presumed to be low, it is apparent that this is the age when infection begins (3).

Unlike all the other neglected tropical diseases that had their disability-adjusted life years (DALYs) lowered during the period 1990 to 2010, DALY for schistosomiasis has increased by 55.7% (9). Schistosomiasis affects people residing in poverty-stricken areas for up to half of their lives . The new global interest to eliminate schistosomiasis as a public health problem by 2025 (65th WHA, 2012) advocates targeting school age children (SAC) (10), while neglecting preschool age children (PSAC), due to assumed lack of exposure to infection.

An estimated 50 million PSAC need treatment but fail to access it because they are excluded from national schistosomiasis control programs (11). PSAC are neglected because of difficulties in obtaining parasitology for diagnosis, difficulties in detecting light infections and inadequate knowledge about risk factors associated with the infection in this age group. It is usually assumed

84 that the impact of schistosomiasis on health and associated morbidities in this age group are
85 negligible (11). Another main reason for excluding the PSAC is because of the lack of a paediatric
86 dose formulation of praziquantel (12). The first encounter with schistosomiasis occurs during the
87 first five years of life (13). This infection then persists, leading to a natural immune system change
88 and increasing morbidity and risk of co-infections; as well as affecting cognition and growth (11). In
89 this article we focus on *S. haematobium* which is highly prevalent in Zimbabwe, and determine the
90 infection burden in a neglected group which is excluded in mass treatment campaigns.

91 Trapped eggs in the human body systems causes much of the morbidity (14). The life cycle of *S.*
92 *haematobium* involves an asexual reproduction phase which occurs in snails of the genus *Bulinus*,
93 and the sexual reproduction phase which occurs in human hosts (15). *S. haematobium* penetrates the
94 human skin as cercariae and loses its tail and becomes a schistosomulum (16). The schistosomula is
95 transported to the organs via the venous and lymphatic systems (17). The schistosomula then enter
96 the lung and pass through the heart on their way to the liver. In the liver, they mature into adult
97 worms and copulate (18). After copulation females then deposit eggs into the vesicular and pelvis
98 venous plexus of bladder (19). The eggs then move to lumen of bladder and ureters where they are
99 eliminated with urine (20).

100 *S. haematobium* is known to cause the following morbidity: haematuria, dysuria, hydronephrosis and
101 bladder wall pathology (1,7,21,22). Due to advances in diagnosis and clinical observation,
102 schistosomiasis has also been associated with genital morbidity, where in adults, it has been linked to
103 acquisition of HIV infection (10,16). Genital schistosomiasis manifests differently in males and in
104 females. In men it manifests as epididymitis which can simulate tuberculosis, hemospermia and
105 prostatitis (10). In women the symptoms are unspecific, but the most frequent are dyspareunia,
106 dysmenorrhea, leucorrhea, menstrual disorders, post coital bleeding, cervicitis, endometriosis and
107 salpingitis. These genital lesions can cause early miscarriages, ectopic pregnancy and infertility (10).
108 The advanced stage includes bladder calcifications, urinary tract fibrosis, obstructive uropathy and
109 bladder malignancies (11,17). Of note is that urogenital schistosomiasis has been associated with

110 increased HIV transmission as it affects the pelvic organs and may also result in abnormal
111 inflammatory reactions to immunizations (17). *S. haematobium* has also been associated with
112 debilitating generalized conditions including malnutrition, anemia, growth retardation, impaired
113 cognition and developmental delays during childhood (23).

114 Morbidity is expected to be higher in individuals with high infection intensity (5,21,24–26). To be
115 specific, children under the age of five have been reported to harbour low infection intensity
116 which results in difficulties in diagnosis (5,7,8,27). Furthermore with schistosomiasis being
117 prominent in tropical areas there are many other infectious diseases that schistosomiasis might
118 mimic (1,28). In this study we demonstrate morbidity associated with *S. haematobium* in children
119 under the age of five years old in an endemic district in Zimbabwe and identify clinical morbidity
120 markers that may be useful in the early diagnosis of schistosomiasis in PSAC.

121

122 **Methodology**

123 **Study site and design**

124 The study was carried out in Shamva district (31°40'0" E longitude and 17°10'0" S latitude) in
125 Mashonaland Central province, Zimbabwe (29). Shamva district has the highest prevalence of
126 schistosomiasis in Zimbabwe at 62.4% (30). It lies 945 m above sea level, the climate is warm and
127 temperament with an average temperature of 20.2 °C and an annual rainfall of 887 mm. Located in
128 the Mazowe valley, Shamva district is an area with high farming activity due to its fertile soil.
129 Residents get their water supply from Mazowe river which spans through the district and is a huge
130 source of alluvial gold which the vast majority of population survives through panning (29). The
131 study was a community cross-sectional survey, children were recruited from 19 different villages in
132 Shamva district gathering at expanded program for immunisation(EPI) centres and Shamva district
133 health centres and hospital.

134

135 **Study inclusion criteria**

136 The participants recruited in the study had to be aged between 1 to 5 years from the Shamva district
137 and met the following inclusion criteria: 1. Be lifelong residents of the study area 2. Had no
138 previous anti-helminthic treatment exposure 3. Parental/guardian consent to participate 4. Be
139 negative for *Schistosoma mansoni* and geohelminths 5. Malaria negative 6. Be negative for the
140 ToRCHeS (toxoplasmosis, rubella, cytomegalovirus, hepatitis and syphilis) screen 7. Be HIV
141 negative 8. Have a widal TO ratio <1:160.

142

143 **Sample size**

144 The required sample size was calculated to be 363 participants using Dobson's formula as follows:

145

146
$$n = \frac{z^2 pq}{e^2}$$

147 Where Z is the Z value for the 95% confidence interval, that is alpha = 5% (z = 1.96)

148 p=proportion/prevalence of the outcome to be investigated (p = 0.62)

149 q=1-p=0.38

150 d = precision for the given confidence interval expected expressed as decimal (d=0.05)

151 n = 363

152

153 **Data collection**

154 A questionnaire was administered in the form of history taking done by clinicians to the
155 caregivers/parents and participants medical records were assessed carefully. In Zimbabwe,
156 children <5 years old report to health centres once every month for general growth monitoring
157 which is recorded on growth cards.

158

159 **Clinical examinations**

160 The clinical examinations were conducted on PSAC (n=416) by three medical practitioners
161 independent of each other who were blinded to the infection status of the participant. The

162 examination of the study participants was holistically done according to a standard protocol adopted
163 from standard clinical practices summarized below(Figure 2) (31,32).

164 **Anthropometry**

165 Height and weight were measured with the participants in light/no clothing. Infantometer baby
166 board was used to measure height and for weight we used a baby scale. Mid Upper Arm
167 Circumference (MUAC) : measurement was done on the left arm mid-point between the shoulder
168 and the elbow tip, with the arm relaxed and hanging down the body. Height and weight for age
169 charts as well as the MUAC reading were used to assess nutritional status.

170

171 **Developmental assessment**

172 We used the childhood developmental charts from UNICEF to measure gross motor, fine motor,
173 language and social development.

174

175 **HEENT(Head, eye, ear, nose and throat) Examination**

176 Head: Shape, size, masses, fontanelles; amount, colour, texture and distribution of hair; scar and
177 cleanliness of scalp.

178 Ears: Tragus or mastoid tenderness, tophi, cerumen, light reflex, bulging, retraction and perforation
179 of tympanic membrane.

180 Eye: periorbital oedema, ptosis, lid lag and conjunctival pallor.

181 Nose: Deformities, deviation and perforation of septum, polyps and unusual discharges .

182 Mouth and throat: Breath odour; colour, fissures and ulceration of lips; bleeding, ulceration, and lid
183 line of gums; tooth caries; tongue colour, coating, fissure, papillae atrophy; colour, ulceration,
184 tumour, monilial patches of buccal mucosa and soft palate; tonsillar inflammation and exudates.

185 **Lymphatic system examination**

186 Lymph nodes: Site, size, consistency, tenderness, fixation, discrete or matted, regional or
187 generalized enlargement

188 **Respiratory system**

189 Inspection: Cyanosis of lips and nails, clubbing of fingers, rate, depth and character of respiration,
190 symmetry of shape and expansion, use of accessory muscles, retractions.

191 Palpation: Tenderness, subcutaneous crepitation, position of trachea, degree of chest expansion (in
192 cm with tape or hand grip), tactile fremitus.

193 Percussion: percussion notes (resonance, hyper-resonance, dull, flat), diaphragmatic excursion

194 Auscultation: Character of breath sounds (vesicular, bronco-vesicular, bronchial, tracheal), crackles,
195 wheezing, friction rub, vocal resonance.

196 **Cardiovascular system**

197 Arteries: pulse rate, rhythm, volume, character, radio-femoral delay (Carotid, Brachial Radial,
198 Femoral, Popliteal, Dorsalis pedis and Posterior tibialis).

199 **Precordium (Heart) examination**

200 Inspection: Presence of precordial bulging, active or quiet precordium, location of apical impulse
201 (interspace, distance from left midclavicular line)

202 Palpation: Point of maximal impulse and its character, parasternal heave, thrill, shock Percussion:
203 cardiac outline (not frequently performed)

204 Auscultation: 1st and 2nd heart sounds, 3rd and 4th heart sounds, other added heart sounds
205 (gallop, ejection click, opening snap, pericardial 'knock'), murmur, friction rub

206 **Abdominal Examination**

207 Inspection: Abdominal symmetry, shape (round, flat, scaphoid), movement with respiration, flank
208 fullness, everted or inverted umbilicus, dilated vessels, scars, visible peristalsis, presence of hernia
209 at hernia sites.

210 Palpation: tenderness (superficial or deep, site), rebound tenderness, guarding and rigidity,
211 enlarged liver (size in cm below right costal margin along right midclavicular line, consistency,
212 surface, edge, tenderness), enlarged spleen (size in cm along splenic growth line below left costal
213 margin, consistency, surface, edge, tenderness, splenic (medial) notch), abdominal mass (size,
214 consistency, surface, edge, tenderness, fixation, mobility with respiration), and enlarged kidneys
215 (size, consistency, surface, edge and tenderness by bimanual palpation).

216 Percussion: Total vertical liver span, liver and splenic dullness, shifting dullness, fluid thrill .

217 Auscultation: Bowel sounds, bruit over the liver, friction rub over the liver and the spleen, renal
218 bruit.

219 **Genitourinary system**

220 Costovertebral angle and suprapubic tenderness. In male, scrotum (oedema, hydrocele and hernia),
221 testes (size and descent), vas deferens (nodules, tenderness), varicocele, urethral orifice
222 (reddening, discharge, ulcer, phimosis). In females urethral orifice (reddening, discharge), vaginal
223 discharge, cystocele/rectocele.

224 **Integumentary system**

225 Skin: Texture, rashes, ulcers, urticaria, pigmentation. Hair: texture, Nails: colour, shape (clubbing
226 and spooning), texture, splinter haemorrhages, capillary refill time.

227 **Musculoskeletal system (Locomotor system)**

228 Muscle: muscle tenderness, spasm. Spine: deformity (kyphosis, scoliosis, kyphoscoliosis), gibbus,
229 tenderness on percussion or pressure, limitation of movement. Joints: Swelling, tenderness, heat
230 and redness, crepitus, deformity, limitation of movement on active and passive motions. Bones:
231 deformity, fracture, tenderness.

232 **Nervous system**

233 Level of consciousness (GCS), orientation in time, place and person; speech disturbance
234 (dysphasia).

235 Cranial nerves (CN) one to twelve assessed.

236 **Motor system**

237 Position, bulk, fasciculation (spontaneous or provoked), strength (power), tone, reflex (deep and
238 superficial)

239 **Deep tendon reflexes**

240 Biceps Triceps supinators Patellar Ankle.

241 **Sensory system**

242 Two point discrimination, Finger-to-nose test, heel-to-shin test, supination-to-pronation of
243 forearm.

244 **Sample collection**

245 Urine samples were collected by giving the caregiver a wide open container to let the child urinate
246 in, children 1 year and below used paediatric urine collector attached by a clinician. The caregivers
247 then brought the samples which were examined.

248

249 **Samples processing**

250 Urine samples collected were examined for macrohematuria using the Uristix reagent strips (Uripath,
251 Plasmatec, UK) dipped into fresh, well-mixed urine for 40 sec and the test area was compared with a
252 standard colour chart as per manufacturer's instructions. The parasitology team conducted
253 parasitology examination and results were recorded separately, not accessed by the clinical team.
254 Approximately 50 ml of urine sample was collected from each participant on three consecutive days.
255 The samples were collected between 10am and 2pm and processed within 2 hours of collection by
256 urine filtration method and were examined using microscopy for *S. haematobium* eggs detection. The
257 number of eggs were reported per 10ml of urine. Stool samples were collected on a single day and
258 processed using the Kato Katz method with 2 slides prepared per sample, parasite eggs were
259 enumerated under a light microscope for *S.mansoni* in duplicate per gram of stool. A formal ether
260 sedimentation technique was used to test for geohelminths presence (33).

261

262 Plasma and sera were obtained from blood collected in well-labeled EDTA and coagulant-free blood
263 collection tubes respectively. Samples from each child were processed and tested for
264 toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus 1 and 2, HIV and hepatitis. The sera
265 was processed using the Maglumi 4000 chemiluminescence immunoassay analyser (CLIA). Children
266 noted to have infection were managed appropriately by the doctors in the study and the
267 community nurse. Thick blood film slides were stained using the Geimsa stain and examined for
268 malaria parasites using microscopy.

269

270 **Ethical statement**

271 Ethical approval was obtained from Medical Research Council of Zimbabwe (MRCZ/A/2435).
272 Gatekeeper approval was obtained from the Provincial and District Medical Directors and
273 Community Leaders. Informed consent was obtained from the parents or guardians of the children.
274 All participants with confirmed infection were offered treatment.

275

276 **Statistical method**

277 Data analysis was performed using STATA version 15. The statistical methods applied included the
278 descriptive statistics, bivariate analysis using odds ratio and multivariate logistic regression
279 modelling. In this study we determined how much of the detected morbidity was attributable to *S.*
280 *haematobium* infection by elucidating Prevalence Ratios (PRs). The morbidity markers were selected
281 based on them having a $PR > 1$, which shows a significant association with *S. haematobium* infection.
282 The multivariate logistic regression models were fitted to adjust for potential confounding factors for
283 the five manifestations with three explanatory variables; that is sex, age and schistosomiasis
284 infection. The effect of different factors on the prevalence of schistosome infection and morbidity
285 was determined using logistic regression and the results reported as adjusted ORs (AORs) and 95%
286 confidence interval (CI), along with the test for significance, as previously described (34). Infection
287 intensity for *S. haematobium* was defined as the arithmetic mean egg count/10ml of at least two urine
288 samples collected on three consecutive days .

289

290 **Results**

291 **Demographics**

292 A total of 416 children from 19 villages in Shamva district, Mashonaland central in Zimbabwe were
293 included into the study (Figure 1). The number of males was 214 (51.4%) and the difference in sex
294 composition was not statistically significant ($p=0.20$). Age was normally distributed (Shapiro Wilk
295 test, $p=0.068$) and the range [min-max] was [1-5] years with mean \pm (SD) age of 3.39 ± 1.08 years.

296

297 **Morbidity observed in the study participants**

298 Clinical features observed in the study participants were as follows: 8% (36) had hematuria, 36%
299 (149) had inguinal lymphadenopathy, 19% (81) had ascites, 19% (79) had wheezes, 11% (46) had
300 shortness of breath, 4% (20) had an atopy history, 10% (43) had malnutrition and 18% (75) had
301 stunting
302 (Table 1).

304 ***S. haematobium* epidemiology**

305 The overall *S.haematobium* infection prevalence was 35.1% (146). When segregated by sex,
306 schistosomiasis prevalence was higher in females 37.1% (75/212) were positive compared to males
307 with a prevalence of 33.2% (71/214). A greater proportion of females were infected at the ages of 2,
308 3 and 4 years with more males being infected at 1 year and 5 years. The likelihood of developing
309 schistosomiasis increased with age (Figure 3).

311 **Characterizing Schistosomiasis Morbidity in Children under the Age of Five Years**

312 Children with *S. haematobium* were at greater odds of presenting with the following: haematuria
313 (Adjusted Odds Ratio (AOR) = 12.6 95%CI 11.6 to 14.1), inguinal lymphadenopathy (AOR = 99.2
314 (95%CI 24.2 to 854.5), Ascites (AOR=23.9 (95%CI 11.4 to 54), wheezes (AOR = 35.4 (1.72
315 (95%CI 15.3 to 94.2), shortness of breath (AOR = 1.72(95%CI 0.87 to 3.35), atopy history AOR =
316 5.6 (95%CI 1.85 to 20.2), malnutrition (using weight for age and height for age charts) AOR =
317 1.8(95%CI 1.3 to 3.2), malnutrition (using MUAC tape) AOR = 2.3 (95%CI 1.4 to 3.2) and stunting
318 (AOR = 1.9 (95%CI 1.1 to 2.2) (Table 2).

320 Morbidity attributable to *S.haematobium* was noted to be high for Inguinal lymphadenopathy (
321 Attributable Fraction (AF) = 68.4% (95%CI 65.9 to 70.2), haematuria (AF = 92.6% (90.5 to 95.3),
322 ascites (AF = 91.5% (95%CI 88.5 to 94.9), wheezes (AF = 93.9% (95% CI 90.1 to 96.2), shortness
323 of breath (AF = 35.9 (95%CI 31.2 to 36.8), Atopy history (AF = 76.9 (95%CI 75.2 to 78.5),

malnutrition(using MUAC tape) (AF = 20% 95%CI 10 to 40) malnutrition (using weight for age and height for age charts) AOF = 20% 95%CI 10 to 40), Stunting (AF = 38.2 (95%CI 16.7 to 61%)) (Table 3).

The inguinal lymph nodes observed were rubbery, immobile, non-tender and >2cm in size. A relationship indicating that an increase in schistosomiasis infection is associated with a corresponding increase in inguinal lymphadenopathy prevalence in children who were *S.haematobium* infected was observed at each area (site) (Figure 4). An association between the likelihood of lymphadenopathy and the likelihood of schistosomiasis infection was also proven (Figure 5).

334
335

336 Discussion

To our knowledge, this is the first study reporting on different morbidity markers associated with *S haematobium* infections in PSAC. We found a positive association between *S. haematobium* infection with the following: inguinal lymphadenopathy, wheezes and crackles, ascites, an atopy history, haematuria and nutritional status. Inguinal lymphadenopathy, wheezes, ascites and atopy history have not been previously noted as *S. haematobium* morbidity markers.

342

To our knowledge this is the first study to identify the strong association between schistosomiasis and inguinal lymphadenopathy. There was a five-fold higher odds of having Schistosomiasis among those who presented with inguinal lymphadenopathy than among those without the infection. Most of the other common causes of lymphadenopathy (35) (including tuberculosis and HIV) in the population were excluded, strengthening confidence in our findings. In a study in Zimbabwe among the general population, 4% of the lymph node samples had non-tuberculous inflammatory changes. Most of the nodes were from patients aged one to fifteen years in rural hospitals. In literature, *S. haematobium* has not been linked to lymphadenopathy, though *S. mansoni* and *S. japonicum* have

351 been recorded to cause enlarged abdominal lymph nodes (36–38). We present novel findings to
352 suggest that this may have been partly due to schistosomiasis (35). Involvement of regional lymph
353 nodes in schistosomiasis infected mice have been noted in *S. mansoni* infection (36). The association
354 of inguinal lymphadenopathy with *S. haematobium* requires further investigation on the
355 immunopathological manifestation.

356

357 The lungs have not previously been understood to be an end organ of schistosomiasis morbidity
358 manifestation (2,39,40). We found strong associations between *S. haematobium* infection and
359 respiratory morbidity among PSAC. *S. haematobium* infected children had wheezes and crackles in
360 the chest on auscultation, with a 35-fold higher odds of respiratory morbidity. Acute schistosomiasis
361 is known to present as shortness of breath, wheezing, and a dry cough and is said to happen in
362 *Schistosoma* naïve travellers (41) Similar findings in children from an endemic area suggest
363 comparable immunological naivety. Chest X-rays of people with pulmonary schistosomiasis show a
364 millary mottling resembling millary tuberculosis or midzone infiltrates and condensed basilar zones
365 (28). In areas like Zimbabwe, where schistosomiasis is endemic, TB is also prevalent making a
366 diagnosis of pulmonary schistosomiasis difficult as clinicians are more likely to diagnose TB than
367 neglected tropical diseases (28). In our study TB was an exclusion criterion. Our finding makes it
368 crucial for clinicians and policymakers to be alerted, as this has the capacity of reducing under-fives
369 morbidity vastly thus improving their quality of life.

370

371

372 *S. haematobium* is not previously correlated to abdominal morbidity, in our study we found an
373 attributable fraction of 91.5 % with a PR of 11.8 to ascites in schistosomiasis positive PSAC. The
374 odds ratio of the positive children presenting with abdominal distension and ascites was noted to be
375 21.9 (95% CI 10.9 to 44) with a p-value of <0.001) For the first time we have demonstrated ascites
376 in *S. haematobium* infected children without *S. mansoni* or geohelminths as co-infections, or any
377 other possible causes of ascites after a thorough work up. Furthermore, the children were treated by a

378 single dose of praziquantel (at 20mg/kg) and on follow-up the ascites had resolved without any
379 further intervention. The infected individuals started with what appeared like a pot belly as in Figure
380 6. Further follow up with an ultrasound scan would be beneficial and further bio-chemical evaluation
381 of the ascitic fluid would be very valuable.

382

383 Contrary to previous reports of an inverse relationship between schistosomiasis and atopy, infected
384 children had a 6-fold higher odds of presenting with atopy (6,42,43). It has been reported that
385 schistosomiasis in PSAC is usually at low intensities and this might explain why we had a positive
386 relation (5). Further immunological studies are necessary to understand the higher odds ratio we
387 reported.

388

389 Our study provided additional evidence of the relationship between schistosomiasis and haematuria
390 (7,16,18,20,34). The observed haematuria is secondary to eggs being lodged in the bladder wall.
391 However, due to low intensity of infection in the PSAC, macrohematuria is not often detected by the
392 caregiver that makes the health seeking habits due to *S. haematobium* in this age group very poor
393 (34). We recommend that caregivers and medical professions in endemic areas be made aware of the
394 other signs and symptoms to look out for in infected PSAC, in-order to avoid this bias.

395

396 Nutritional status has been shown to be affected by *S. haematobium* status in PSAC and even in
397 SAC. The process starts in the womb during pregnancy, infected mothers expose their foetuses to
398 chronic inflammation which may result in low birth weight babies (13). After birth the baby is still
399 exposed to inflammatory markers and once the baby can sit they become exposed to contaminated
400 water when the caregiver takes them to a water source whilst doing house chores (13,27). Chronic
401 exposure to inflammatory markers has been associated with malnutrition (44). In this study we report
402 that malnutrition and stunting had the lowest attributable factors even though they are the most
403 frequently described in association with schistosomiasis morbidity (1,5,8,15,22,27,42).

404

405 The strength of this study included the fact that although the calculated sample size was 368, we
406 managed to enrol 416 participants. We were also able to exclude other major endemic conditions
407 from the area, increasing the likelihood that the morbidities were due to *S. haematobium*. While there
408 is a small chance that some excluded conditions were actually false negatives, we followed study
409 protocol, repeating all tests at least twice. Another limitation is that we only excluded the main
410 known endemic conditions in the area, and there is a chance that some participants had other
411 infection altogether. This is unlikely as the white cell count and C-reactive proteins in all
412 *S. haematobium* negative enrolled participants were within the normal ranges.

413

414 **Conclusion**

415 To achieve the 2025 goal of eliminating schistosomiasis, there is an urgent need for early
416 schistosomiasis diagnosis. The morbidity markers described in this paper can be used to increase the
417 index of *S. haematobium* suspicion in PSAC within endemic areas. In this study it was found that *S.*
418 *haematobium* in PSAC contrary to popular belief does not only affect the genitourinary system. For
419 the first time it was noted that it also affects the respiratory, gastrointestinal and lymphatic system.
420 An interesting relationship was noted between Schistosomiasis and atopy. It is important that
421 clinicians in schistosomiasis endemic areas be alerted of these morbidity markers of *S. haematobium*
422 in order to increase indices suspicion for schistosomiasis in pre-school age children.

423

424 **Data Availability**

425 The statistical data on the parasitology and clinical scores used to support the findings of this study
426 are available from the corresponding author upon request.

427 **Conflict of Interest**

428 The authors declare that there is no conflict of interest.

429

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435

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442

443 **Author Contributions**

444 TLMJ, FM TN and TM conceived and designed the study. TLMJ, LJ, MK, EC, HM, AV, SR, ENS, ,
445 KM, FM, TN and TM performed the clinical examination or parasitology and the data analysis.
446 TLMJ wrote the first draft and all authors contributed to the manuscript and revised the final version.

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542 months compliance study. 2018;1–16.

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550 **Table 1: Distribution of clinical morbidities in pre-school aged children(1-5 years old).**

Clinical Features		Schistosomiasis Infection (eggs in urine) Status		Totals % (n)
		Infected	Not infected	
Haematuria	Positive	24	12	9% (36)
	Negative	122	258	91% (380)
Inguinal lymphadenopathy	Present	95	54	36% (149)
	Absent	52	215	64% (267)
Ascites	Present	71	10	19% (81)
	Absent	76	259	81% (335)
Sounds in the chest	wheezes	72	7	19% (79)
	Clear	75	262	81% (337)
Respiratory rate	Shortness of breath	22	24	11% (46)
	Normal	125	245	89% (370)
Atopy History	Yes	15	5	5% (20)

	No	132	264	95% (396)
Malnutrition (weight and height for age charts)	Yes	17	17	8% (34)
	No	123	259	92% (382)
Malnutrition (MUAC)	Yes	5	4	2% (9)
	No	174	233	98% (407)
Stunting	Yes	38	37	18% (75)
	No	71	270	82% (341)

***Significant at 5% level of significance (p=<0.05)**

Table 2: Adjusted Odds Ratio of clinical features associated with *S. haematobium* morbidity

Clinical features	Adjusted odds ratio (AOR)	95% Confidence Interval
Haematuria	21.8*	(11.7- 40.7)
Inguinal lymphadenopathy	4.63*	(2.21-5.96)
Ascites	23.9*	(11.4-54)
Wheezes and crackles	35.4*	(15.3- 94.2)
Tachypnoea with Shortness of breath	1.72*	(0.87-3.35)
Atopy History	5.6*	(1.85-20.2)
Malnutrition (weight and height for age charts)	1.8*	(1.3-3.2)
Malnutrition (MUAC)	2.3*	(1.4-3.2)
Stunting	1.9*	(1.1-2.7)

***Significant at 5% level of significance (p=<0.05)**

Table 3: Morbidity Attributable to *S. haematobium* infection

Morbidity	Diagnostic Method	PR (95%CI)	Attributable Fraction (Infected)95%CI
Inguinal lymphadenopathy	Palpation in the lymph nodes area	3.16 (2.34-4.56)	68.4 (65.9-70.2)
Haematuria	Urine dipsticks	12.6 (11.4-14.1)	92.6 (90.5-95.3)
Distended Abdomen with shifting dullness (ascites)	Gastrointestinal system clinical examination	11.8 (9.23-13.2)	91.5 (88.5-94.9)

Wheezes and crackles	Respiratory system clinical examination	16.4 (13.5-20)	93.9 (90.1-96.2)
Tachypnoea with shortness of breath	Observation and respiratory rate	1.56 (1.02-3.11)	35.9 (31.2-36.8)
Atopy History	Questionnaire	4.32 (3.67-6.89)	76.9 (75.2-78.5)
Malnutrition (MUAC)	MUAC tape	1.2 (0.7-1.9)	20 (10-40)
Malnutrition (WHZ)	Weight for height WHO child growth charts	1.0 (0.8-1.4)	5 (0.0-40)
Stunting	Height for age from WHO child growth charts	1,7 (1.1-2.7)	38.2 (16.7-61)

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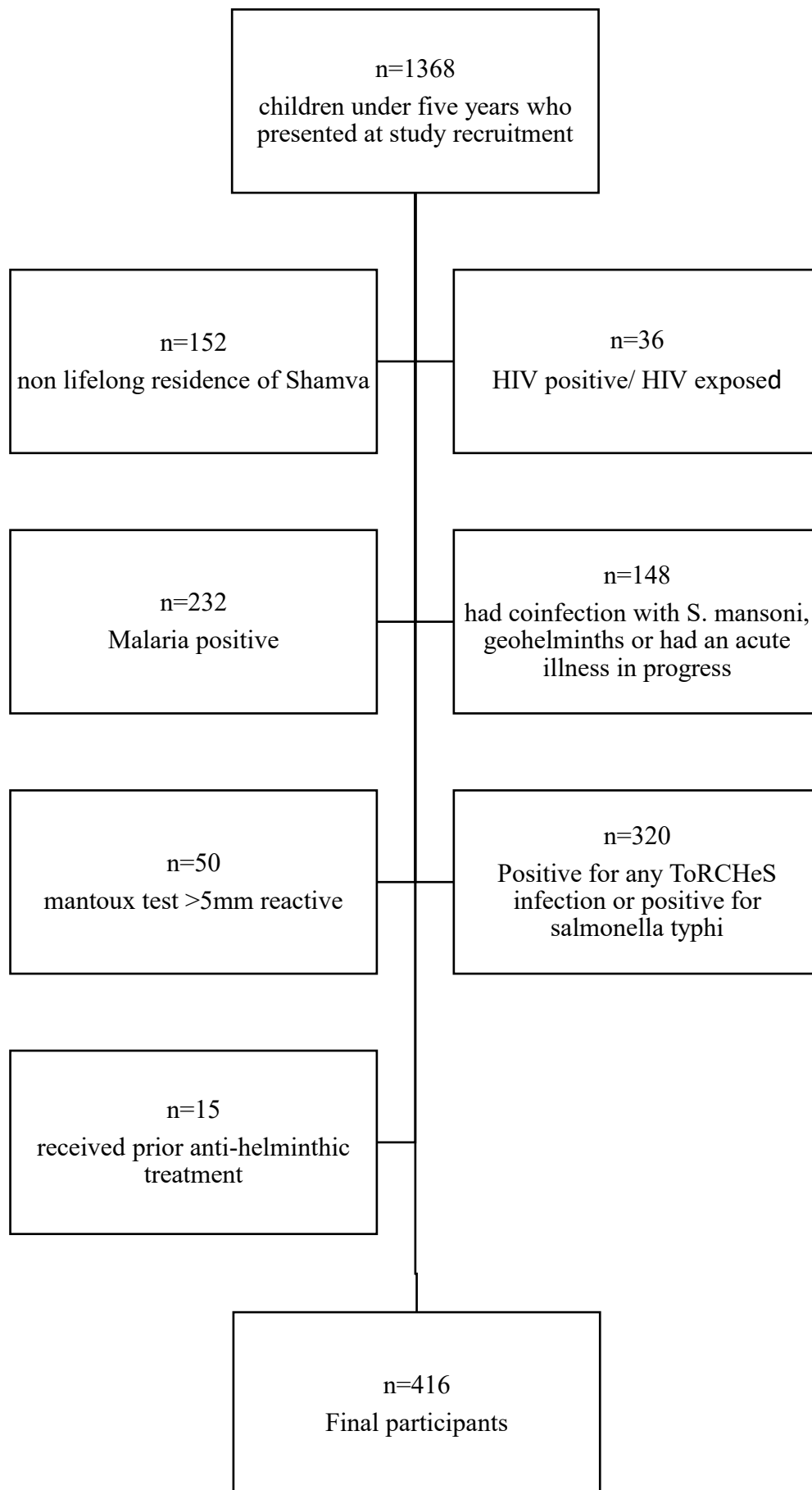


Figure 1: Flow diagram showing the selection steps of the study population and the exclusion criteria

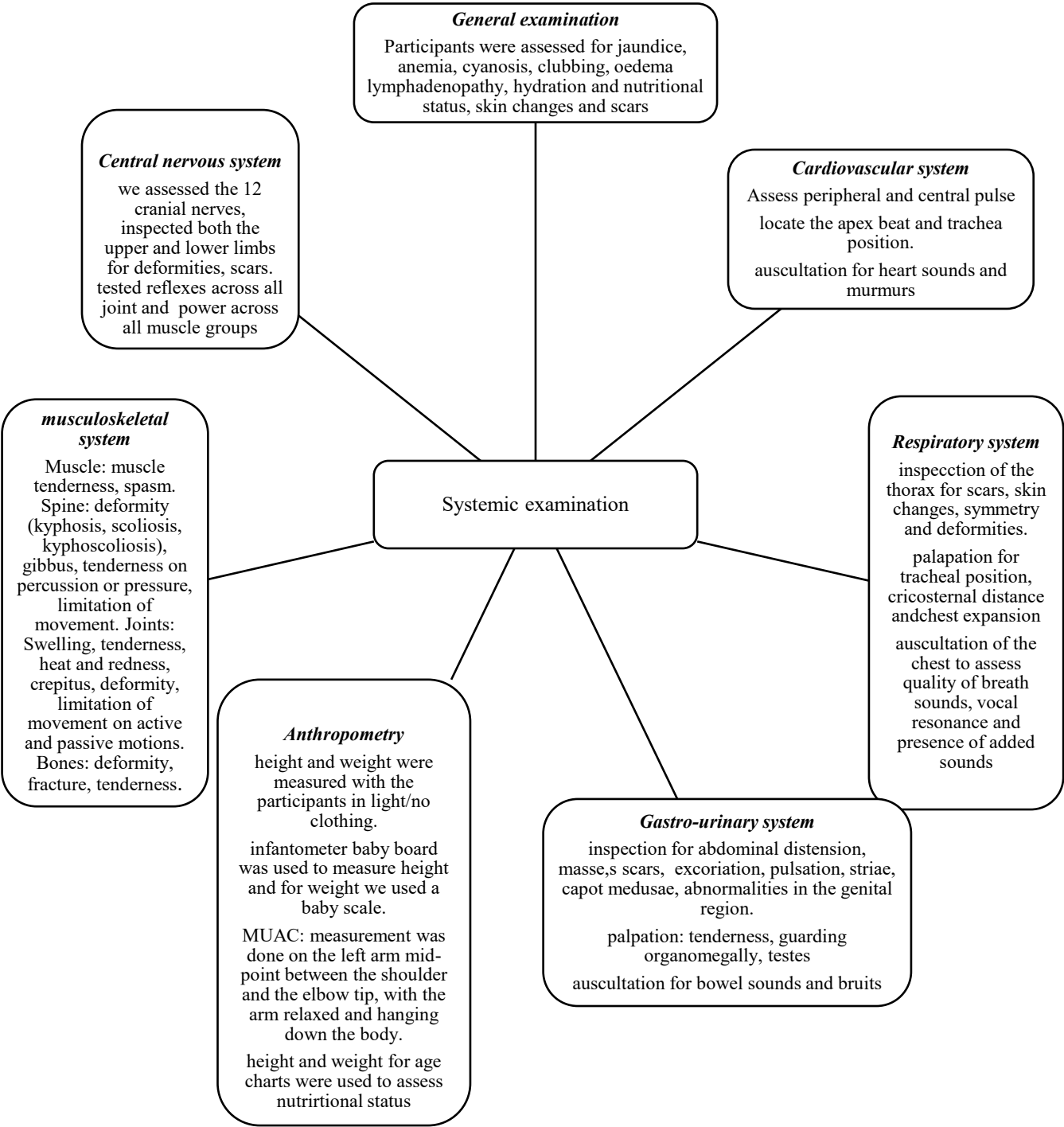


Figure 2: Showing the methodology protocol used for the systematic examinations conducted by the 3 clinical members independent of each other and without the knowledge of parasitology diagnostic outcome by urine filtration for *S. haematobium* ova.

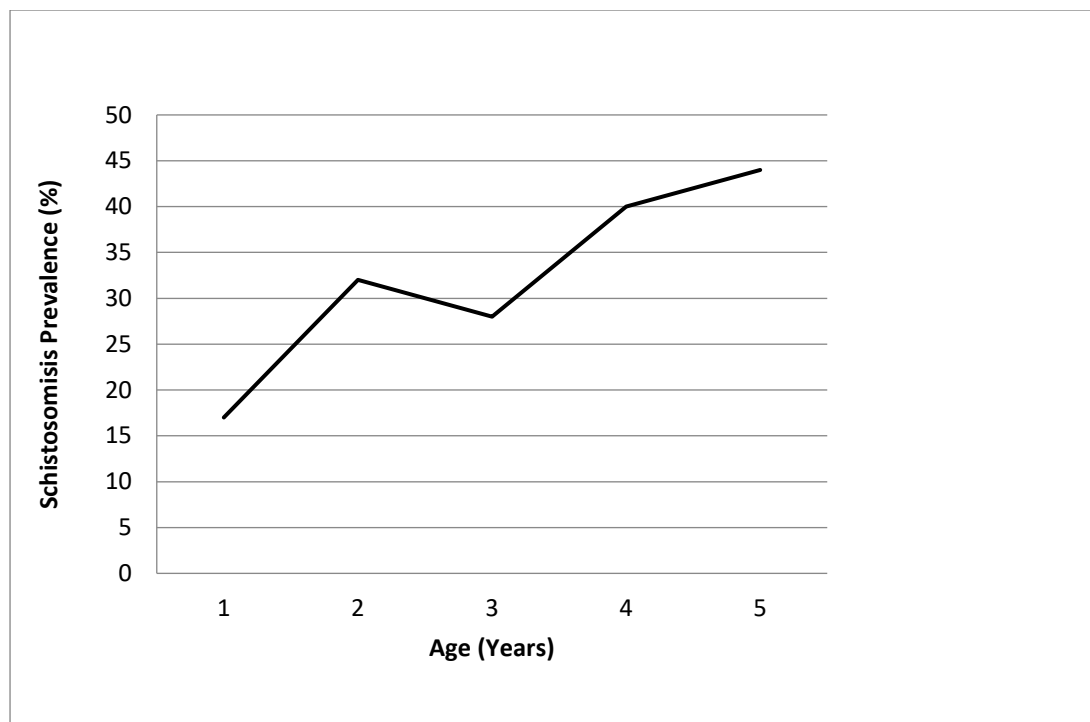


Figure 3: Schistosomiasis prevalence pattern according to the age of the child.

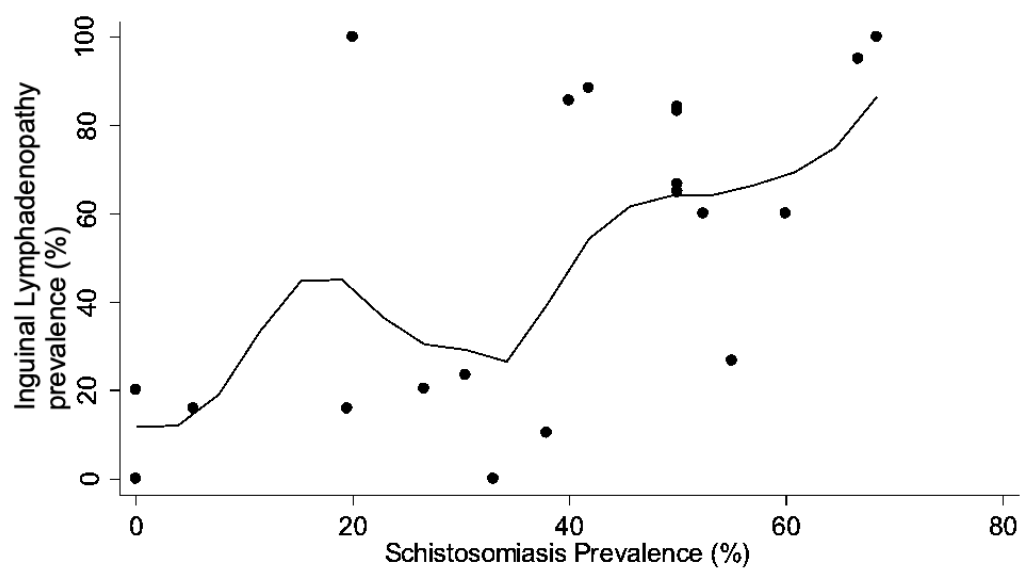


Figure 4: The association between schistosomiasis prevalence and inguinal lymphadenopathy prevalence observed at each area (site)

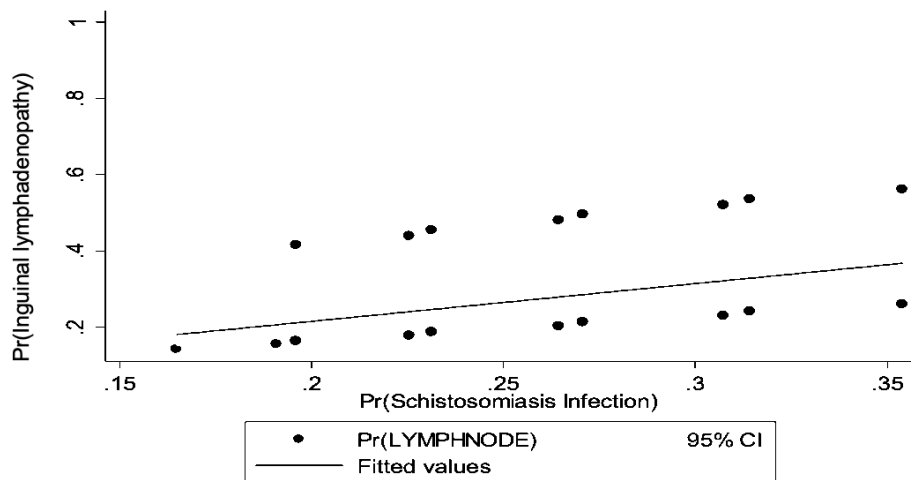
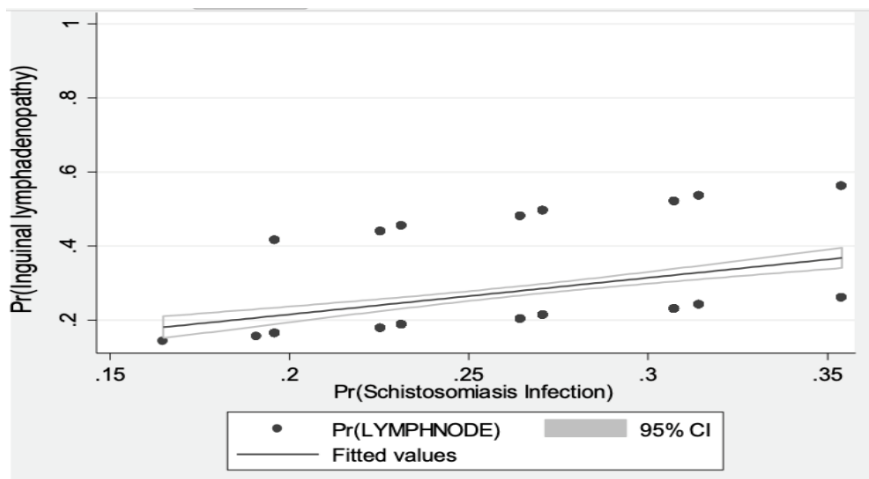


Figure 5: Probability(Pr) of Schistosomiasis Infection and inguinal lymphadenopathy Development



603 Figure 6: A 4 year old child with *S. haematobium* infection with no *S.mansoni* infestation.

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